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ORIGINAL ARTICLE

A model-based analysis to guide gonadotropin-releasing hormone receptor antagonist use for management of endometriosis

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Aims: To identify linzagolix doses, an oral GnRH receptor antagonist, that effectively lower oestradiol (E2) to relieve endometriosis-related pelvic pain without compromising bone health.
Methods: Integrated statistical, pharmacokinetic–pharmacodynamic and systems pharmacology models were developed from Phase 1 and 2 clinical trial data in healthy volunteers and patients, receiving linzagolix 25–200 mg daily or placebo, and analysed simultaneously. The main outcome measures were pelvic pain scores for dysmenorrhoea, nonmenstrual pelvic pain (NMPP), uterine bleeding and lumbar spine bone mineral density (BMD).
Results: Linzagolix pharmacokinetics were described by a 2-compartment model with sequential zero/first-order absorption process (CL/F: 0.422 L/h). E2 changes over time were well described as a function of linzagolix 24-hour AUC (AUC_{50}: 1.68×10^5 ng h/mL). For a Caucasian reference patient, a change in E2 from 50–20 pg/mL at 24 weeks increased the odds of relief of dysmenorrhoea 1.33-fold and NMPP 1.07-fold (95% CI: 1.22–1.47 and 1.02–1.12, respectively) and decreased bleeding days by 1.55 (95% CI: 1.39–1.72). A previously validated quantitative systems pharmacology BMD model was adjusted to the clinical data. The mean week 24 lumbar spine BMD change from baseline ranged from −0.092% in the 50 mg dose, −1.30% in the 100 mg dose group and −2.67% in the 200 mg dose group.
Discussion: The previously-reported E2 target range (20–50 pg/mL) to balance efficacy and safety endpoints was confirmed. Linzagolix once daily doses between 75–125 mg daily were expected to meet endometriosis-associated pain, efficacy, and BMD loss targets in Caucasian patients.

KEYWORDS
endometriosis, GnRH antagonist, linzagolix

There is no principal investigator for this paper.

1 | INTRODUCTION

Endometriosis is an oestrogen-dependent, painful, chronic disorder affecting 6–10% of reproductive age women caused by implantation of endometrial tissue and its subsequent ectopic extrauterine growth.[1] Oestrogen stimulates local and systemic inflammation, and promotes implantation and maintenance of endometrial tissue in the peritoneum, playing an important role in endometriosis pathophysiology.[1–4] The main symptoms of endometriosis include dysmenorrhoea (DYS), nonmenstrual pelvic pain (NMPP), dyspareunia, pain with urination or bowel movements, and infertility.[2]

Several therapeutic options are available for treating the symptoms and the underlying pathophysiology of endometriosis. Nonsteroidal anti-inflammatory drugs can help control inflammation and pain symptoms. Combination oral contraceptives or progestins can provide relief by inhibiting ovulation to impede the proliferation of endometrial tissue and bleeding during the menstrual cycle.[5]

Gonadotropin-releasing hormone (GnRH) agonists offer another hormonal therapeutic approach for treatment of endometriosis, often used in patients with severe disease who are no longer responding to oral contraceptives.[6,7] GnRH agonists, however, can cause an initial surge of follicle-stimulating hormone, luteinizing hormone (LH), and circulating oestrogen at the start of therapy and paradoxically precipitate a flare in the disease and symptoms. With continued administration, GnRH agonists eventually desensitize **GnRH receptors** in the pituitary gland, resulting in complete suppression of circulating oestradiol (E2) and subsequent inhibition of growth of endometrial implants. Decrease in oestrogen under continued GnRH agonist therapy can be so severe that hypoestrogenic effects, including menopausal symptoms in the short term and osteopenia in the long-term, can become problematic. The extent of bone demineralization due to hypoestrogenaemia is proportional to time and limits the duration of GnRH agonist monotherapy to 6 months. Hormonal add-back therapy (ABT) with an oestrogen and progestogen or progestogen alone, commonly co-administered with GnRH agonists, partially replenishes the circulating oestrogen to prevent bone mineral density (BMD) loss and vasomotor symptoms.

Therefore, antioestrogenic interventions must reduce oestrogen levels enough to affect the pathogenesis of endometriosis, while maintaining a minimum level of circulating oestrogen to prevent hypoestrogenic adverse effects. This balance according to the oestrogen threshold hypothesis[8] and previous quantitative systems pharmacology (QSP) work by Riggs *et al.* found partial suppression of E2 (serum levels between 20 and 50 pg/mL) as a starting point for target E2 ranges.[9] In contrast to GnRH agonists, GnRH antagonists can produce immediate reductions in follicle-stimulating hormone, LH, and circulating oestrogen, avoiding the initial disease flare. Additionally, since the GnRH antagonists act directly on GnRH receptors in the pituitary gland, the antagonist can be optimally dosed to reduce oestrogen, mitigate adverse bone health sequelae from hypoestrogenaemia, and potentially prevent the need for ABT. In 2018, the Food and Drug Administration approved the first oral GnRH receptor antagonist indicated for management of pain associated with endometriosis in over a decade. The antagonist exhibits rapid, sustained, dose-dependent reduction in E2 and correspondingly in BMD and NMPP at month 3.[2]

Integration of pharmacokinetic (PK), PK–pharmacodynamic and QSP modelling has proven to be particularly well-suited for the evaluation of bone-related responses as a part of model-informed drug development.[10] Quantification of relationships between exposure, E2 changes and clinical outcomes could help the selection of safe and effective GnRH receptor antagonist dosing regimens. Linzagolix (also known as OBE2109, KLH2109), an oral nonpeptide small molecule, is a potent and selective GnRH receptor antagonist under investigation for management of endometriosis associated pain.[11,12] The goal of this analysis was to guide linzagolix dose selection for Phase 3 studies enrolling Caucasian patients with endometriosis.

Linzagolix exhibits prompt dose-dependent suppression of E2 with rapidly reversible effects (since ovarian activity tends to resume within 2 weeks from the end of treatment). Linzagolix has high oral bioavailability, a low volume of distribution, and is rapidly and completely absorbed, highly protein-bound (>95%) with no interaction seen with plasma protein binding of other drugs (i.e., warfarin, diazepam, digoxin), metabolized mainly by liver cytochrome P450 enzymes and predominantly excreted in faeces. An integrated modelling approach involving statistical, PK–pharmacodynamic, and systems pharmacology modelling and simulation were used in this analysis to evaluate the balance of linzagolix safety and efficacy signals for optimal dose selection.

What is already known about this subject

- Linzagolix is an oral GnRH receptor antagonist in development for the treatment of endometriosis and uterine fibroid symptoms that works by dose dependently reducing oestradiol and thus allows balancing efficacy with minimizing adverse effects to bone health for successful dosing.

What this study adds

- This integrated modelling and simulation study indicated that linzagolix can target oestradiol ranges appropriately to maximize efficacy without the need of hormonal add-back therapy to protect bone health and determined linzagolix 75 mg daily as an optimal dose regimen for consideration in pivotal Phase 3 endometriosis trials.

TABLE 1 Clinical studies for model development

Study number and title	Endpoints	Population	Linzagolix doses studied	Duration
KLH1101 A double-blind, randomised, placebo-controlled, first in human study to assess the safety, tolerability, PK, PD of oral KLH-2109 and the effect of food in healthy Caucasian female post- and premenopausal subjects after single and multiple ascending oral doses	PK: d 1 and 9	49 (SAD) and 42 (MAD) healthy pre- and postmenopausal women	SAD: 12.5, 25, 50, 100, 200, 400 mg ×1 MAD: 100, 200, 400 mg daily ×7	1–8 d
EDELWEISS NCT02778399 A randomized, double-blind, placebo-controlled, phase 2b dose-ranging study to assess the efficacy and safety of OBE2109 in subjects with endometriosis associated pain	PK: predose, 1.5–2 hr postdose on d 1, predose at wk 4 and 16, and postdose at wk 8, 12, 20 and 24 Pelvic pain: VRS for pelvic pain: no, mild, moderate, severe E2: d 1 and wk 4, 8, 12, 16, 20, 24, 28, 36 Bleeding: none, spotting, bleeding, heavy bleeding DXA: baseline, wk 12, 24, 48	330 women aged 18–45 years with endometriosis	Placebo, 50, 75, 100 and 200 mg daily fixed dose groups Titrated dose group: 75 mg daily for 12 wk followed by either 50, 75, or 100 mg daily	24 wk
16-OBE2109-011 A randomized open-label clinical pharmacology study investigating the effect of OBE2109 and add-back therapy on oestradiol PK	PK: predose on d 8, 15, 22, 29, 36; full profile on d 43 E2: predose on d 1, 8, 15, 29, 36 and on d 43 and 55; predose 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 and 24 hours postdose on d 22 Bleeding: none, spotting, bleeding, heavy bleeding	75 healthy women of child-bearing potential	Placebo, 100, and 200 mg daily	42 d
17-OBE2109-008 A phase 1, randomised, open-label, parallel-group, PK/PD study investigating the effect of OBE2109 and concurrent or delayed add-back therapy administration on bleeding pattern of healthy adult female subjects	PK: predose on d 1, 15, 29, 43, 57, 71 E2: predose on d 1, 15, 29, 43, 57, 71 and 84 (the follow-up visit) Bleeding: none, spotting, bleeding, heavy bleeding	32 healthy women aged 18–48 years	Placebo, 100 and 200 mg daily; 1 mg/0.5 mg add-back	70 d
KLH1204 NCT02778919 A phase 1, randomised, open-label, parallel-group, PK/PD study investigating the effect of OBE2109 and concurrent or delayed add-back therapy administration on bleeding pattern of healthy adult female subjects	PK: 2 hours postdose at wk 0 and 4, and predose at wk 4, 12, 12, 16, 20 and 24 and postdose at wk 8 VRS for pelvic pain: absent, slight, mild, moderate, severe E2: d 1 and wk 4, 8, 12, 16, 20, 24 Bleeding: spotting, mild, comparable to menses, severe DXA: baseline, wk 12, 24	440 Japanese women with endometriosis	Placebo, 25, 50, 75, 100 mg daily	24 wk

Abbreviations: DXA, dual-energy X-ray absorptiometry; E2, oestradiol; MAD, multiple ascending doses; PD, pharmacodynamic; PK, pharmacokinetic; SAD, single ascending doses; VRS, verbal rating scale.

2 | METHODS

2.1 | Data

Data were pooled across 5 clinical trials conducted in healthy volunteers (HVs) or patients with endometriosis, or endometriosis and uterine fibroids. Robust PK data from Phase 1 studies in Caucasian and non-Caucasian HVs (KLH1101, 16-OBE2109-011, 17-OBE2109-008, and KLH1204) and sparse PK data from Phase 2b EDELWEISS study in patients and HVs (Table 1) was incorporated. Patients in the EDELWEISS study received doses ranging from 25 to 200 mg once daily for 24 weeks and HVs received 100–200 mg once daily for 42–70 days. At least 1 linzagolix PK measurement and 1 E2 measurement (measured at each study visit) were required for data inclusion in the analysis.

The population PK analysis data set included 4250 linzagolix concentration observations from 756 subjects, approximately 24% of subjects and 55% of observations were from HVs. The analysis data set for PK-E2 modelling included 4674 E2 observations from 724 subjects, with approximately 15% of subjects and observations as HVs. A summary of the study participants characteristics contributing data to either the population PK analysis set (which did not include subjects receiving placebo doses) or the PK-E2 analysis set (which included subjects receiving placebo doses but did not include HVs in study KLH1101) is shown in Table 3. A full description of the data disposition for each model is provided in the Supporting Information along with an explanation for the methods of covariate selection for the PK model.

The current analysis was intended to guide dose selection in a Caucasian/non-Asian population. While PK, E2 and efficacy endpoints were comparable across different race groups, differences in bone remodelling dynamics across race groups had been previously reported[13] and thus precluded joint analysis of BMD data in Asian and Caucasian populations. The analysis of PK, E2 and efficacy endpoints included both non-Caucasian and Caucasian subjects to reduce parameter uncertainty.

Efficacy endpoints included number of bleeding days, NMPP on nonbleeding days and dysmenorrhoea pain on bleeding days (DYS). For efficacy modelling, daily individual predicted E2 values were averaged across 28-day time intervals (representative of a nominal month) and used as the primary predictor for each efficacy endpoint. More details on efficacy endpoints are given in the Data section of the Supporting Information.

Lumbar spine BMD was measured in patients using dual-energy X-ray absorptiometry (DXA) utilizing GE Lunar or Hologic equipment at baseline, week 12 and week 24 and analysed as the percent change from baseline at weeks 12 and 24. The E2-BMD analysis data set included 401 LS BMD observations in 230 Caucasian patients enrolled in the EDELWEISS study. Mechanistic modelling of the effect of E2 changes on BMD in patients utilized a previously published mechanistic QSP model, following the approach taken by Riggs *et al.*[9]

The NMPP and DYS analysis data set had a total of 619 patients, with 243 subjects in EDELWEISS and 376 subjects in KLH1204. The analysis endpoints for modelling of NMPP and DYS were monthly binary values, categorized by response/nonresponse. Subjects were classified as a responder if the monthly change of NMPP or DYS score achieved a threshold and the use of analgesics did not increase by more than 15% from baseline. Further details are provided in the Supporting Information.

The analysis data set for uterine bleeding included a total of 724 subjects, with 619 endometriosis patients from EDELWEISS and KLH1204 and 105 HVs from studies 16-OBE2109-011 and 17-OBE2109-008. The average number of bleeding days in the 28-day interval at baseline for Caucasian and non-Caucasian subjects was similar, but HVs had 3.56 bleeding days while endometriosis patients had 5.53 bleeding days.

2.2 | Integrated modelling strategy

A decision informatics model-based workflow was implemented to evaluate linzagolix dose candidates for study in Phase 3 clinical trials (Figure 1). All subject data (i.e., HVs and patients) were incorporated into a population PK model to explore dose–exposure relationships and identify sources of variability in PK parameters and concentrations. A second model (PK-E2) evaluated linzagolix exposure (e.g., AUC) and E2 levels, and allowed for

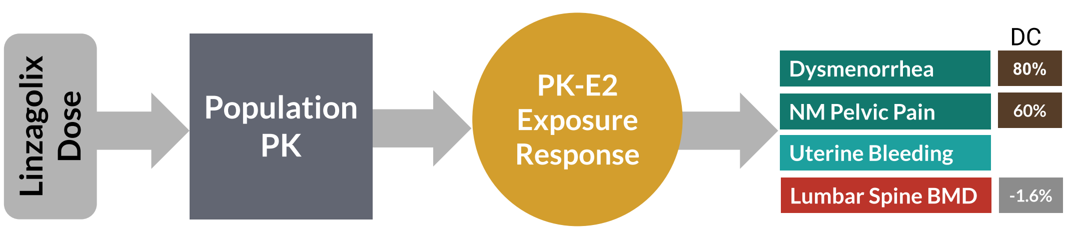

FIGURE 1 Modelling and simulation workflow to evaluate linzagolix doses for testing in pivotal Phase 3 trials. Dysmenorrhoea, nonmenstrual (NM) pelvic pain were efficacy endpoints in the dose decision workflow. Lumbar spine bone mineral density (BMD) was the safety endpoint in the dose decision workflow using a target corresponding to an expected change from baseline of −1.6%. DC: decision criterion; E2: oestradiol; PK: pharmacokinetic

TABLE 2 Targets used for evaluation of linzagolix dose candidates for testing in pivotal Phase 3 clinical trials. All clinical targets were evaluated at week 24

	Target
DYS–VRS (% of responders)	80
NMPP–VRS (% of responders)	60
LS BMD mean CFBL (%)	−1.6

Abbreviations: BMD, bone mineral density; CFBL, change from baseline; DYS, dysmenorrhoea; LS, lumbar spine; NMPP, nonmenstrual pelvic pain; VRS, verbal rating scale.

quantification of differences in HVs and patients. In the third stage, target criteria were established for both efficacy (DYS, NMPP) and safety (BMD) endpoints (Table 2), the basis for different outcome models. The combined set of outcome models were used to simulate clinical endpoints for different candidate linzagolix doses, and the doses that were likely to achieve several (or all) endpoint targets with high probability were identified as candidates for study in pivotal Phase 3 studies. See the Supporting Information for additional software details and model equations.

TABLE 3 KLH1101, 16-OBE2109-011 and 17-OBE2109-008 were conducted in healthy subjects. Subject weight, age and baseline oestradiol (E2) are given as median (standard deviation) calculated from baseline values

Study	Subjects	Percent Caucasian	Weight (kg)	Age (y)	Baseline E2 (pg/mL)
KLH1101	77	70	64.4 (11.2)	40 (15.2)	--
16-OBE2109-011	73	99	62.8 (9.02)	33 (6.95)	25.0 (13.5)
17-OBE2109-008	32	100	64.8 (7.90)	35 (6.64)	20.5 (13.5)
EDELWEISS	244	94	65.5 (17.8)	32 (6.07)	53.0 (7.98)
KLH1204	376	0	53.9 (9.16)	37 (6.47)	44.0 (40.9)
KLH1201	24	0	53.4 (8.03)	35.1 (6.90)	--
KLH1202	109	0	54.1 (6.74)	35.5 (6.62)	--
KLH1203	21	0	53.1 (7.62)	34.7 (6.57)	--

TABLE 4 Parameter estimates for the final population pharmacokinetic model

Parameter	Value	95% CI	Shrinkage (%)
Structural parameters			
CL/F (L/h)	0.422	0.393–0.455	
V2/F (L)	5.13	4.19–6.18	
Q/F (L/h)	0.168	0.130–0.225	
V3/F (L)	3.12	2.83–3.41	
KA (L/h)	2.49	2.04–3.08	
D1 (h)	0.644	0.314–1.24	
Covariate effects			
CL/F ~ non-Caucasian	1.08	1.05–1.12	
CL/F ~ (weight 58 kg)	0.75	FIXED	
V2/F ~ (weight 58 kg)	1.00	FIXED	
Interindividual variability (log-normal)			
IIV-CL/F	0.0354	0.0271–0.0498	16.5
IIV-V2/F	0.0444	0.0203–0.115	62.0
IIV-D1	0.510	0.230–1.41	46.2
IIV-σ^2	0.764	0.505–1.11	24.8
Residual variability (proportional error)			
EDELWEISS data	0.118	0.0698–0.206	
All other studies	0.0389	0.0309–0.0502	

Abbreviations: CI, confidence interval. IIV-σ^2: subject-level variability on the residual error variance; CL/F, clearance; D1, zero-order input duration; KA, absorption rate constant; Q/F, intercompartmental clearance; V2/F, central volume; V3/F, peripheral volume.

2.3 | Simulation to support dose selection for phase 3 trials

Integrated simulations from the PK, PK-E2, pain and bleeding models were used to evaluate candidate doses for study in Phase 3 trials enrolling Caucasian patients with endometriosis. First, target criteria were established for both efficacy (DYS, NMPP) and safety (BMD) endpoints (Table 2). Efficacy criteria were selected considering the confirmatory Phase 3 clinical trial results of another GnRH receptor antagonist at the highest dose (200 mg elagolix, twice daily).[14] The LS BMD target was based on the clinical results of high dose elagolix (300 mg, twice daily), fully suppressing E2 levels, together with a low-dose ABT, a combination that was considered suitable for long-term GnRH antagonist treatment and which resulted in a mean BMD loss of 1.6% (90% CI: −1 to −2.2).[15] PK for each candidate linzagolix dose were simulated and used to drive simulated longitudinal E2 *vs.* time profiles. These simulated E2 data were then used to generate predictions under the DYS, NMPP and LS BMD models 24 weeks after the start of treatment. The probability of meeting the targets of each endpoint was calculated across all replicate simulations for each dose. Doses were evaluated from 0 to 200 mg daily in 25-mg increments. (Table 3)

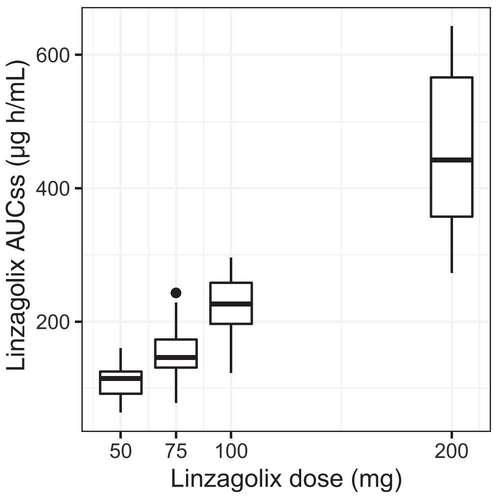

FIGURE 2 Histograms of model-based linzagolix area under the concentration–time curve at steady state (AUCss) for 50, 75, 100 and 200 mg dose groups from the EDELWEISS study. Daily AUC predictions derived from the model were used to drive changes in oestradiol (E2) over time

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[16]

TABLE 5 Parameter estimates for the final pharmacokinetic–oestradiol (E2) model

Parameter	Value	95% CI	Shrinkage (%)
Structural parameters			
Baseline E2, patients (pg/mL)	59.1	52.5–65.6	
Baseline E2, healthy (pg/mL)	26.6	23.3–29.8	
Linzagolix AUC_{50} (ng h/mL)	1.68×10^5	1.44×10^5–1.91×10^5	
Sigmoidicity parameter	1.78	1.49–2.08	
Placebo increase factor	0.65	0.465 –0.834	
Placebo effect rate constant (1/wk)	0.231	FIXED	
E2 increase rate on add-back therapy (pg/mL/wk)	1.58	0.990 –2.16	
Covariate effects			
Baseline E2 ~ (weight 58 kg)	−0.699	−0.958 to −0.441	
Baseline E2 ~ (age 35 y)	0.0829	−0.157 to 0.323	
Baseline E2 ~ non-Caucasian	0.804	0.702–0.907	
Baseline E2 ~ linzagolix drug effect	−0.120	−0.212 to −0.0279	
Interindividual variability (additive on log-scale)			
IIV-baseline E2	0.310	0.262–0.358	11.9
Residual variability (additive on log-scale)			
Patients	0.610	0.571–0.649	
Healthy	0.241	0.179–0.303	

Abbreviation: CI, confidence interval.

3 | RESULTS

3.1 | Data

Linzagolix population PK were best described with a 2-compartment, linear PK model (Table 4) using a sequential zero-order/first-order process (CL/F: 0.422 L/h). E2 changes over time were well described as a function of linzagolix 24-hour AUC (AUC_{50}: 1.68×10^5 ng h/mL). Model-predicted areas under the concentration–time curve at steady state (AUCss) for individuals in the EDELWEISS study are shown in Figure 2. The PK-E2 model estimates revealed approximately 2-fold higher baseline E2 in Caucasian patients relative to Caucasian HVs (Table 5). There was a modest inverse relationship between weight and baseline E2, but no statistically significant relationship was detected between baseline E2 and patient age at baseline (Table 5). Visual predictive check for the E2 *vs.* time data in the EDELWEISS study showed that data simulated from the model were like these E2 observations (Figure 3). Model-based E2 predictions under this model (Figure 4) were used to drive changes in clinical outcome models described below.

The effect of E2 on DYS differed by time interval but generally, lower E2 was associated with a higher probability of DYS and NMPP pain relief (Table 6 and Figure 5). For a Caucasian reference patient, a change in E2 from 50–20 pg/mL at 24 weeks increased the odds of relief of DYS 1.33-fold and NMPP 1.07-fold (95% CI: 1.22–1.47 and 1.02–1.12, respectively) and decreased bleeding days by 1.55 (95% CI: 1.39–1.72). For uterine bleeding, because a direct effect of E2 on bleeding could not be formulated using a single parameter, the effect of change in E2 from 50 to 20 pg/mL at week 24 was computed using simulations in the same manner as for the pain endpoints (Table 7 and Figure 6).

Finally for the safety endpoint, a previously validated QSP BMD model was adjusted to the clinical data. The mean week

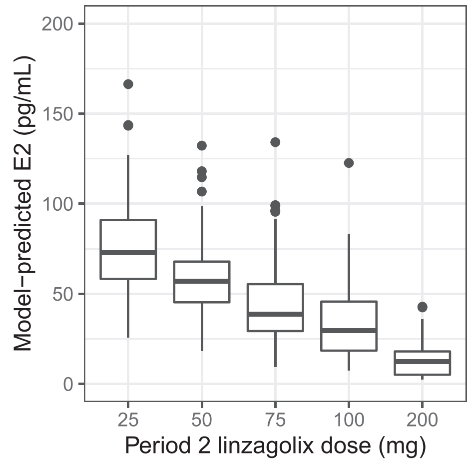

FIGURE 4 Boxplots showing model-based oestradiol (E2) from EDELWEISS and KLH1204 studies at week 24 visit grouped by the period 2 linzagolix dose

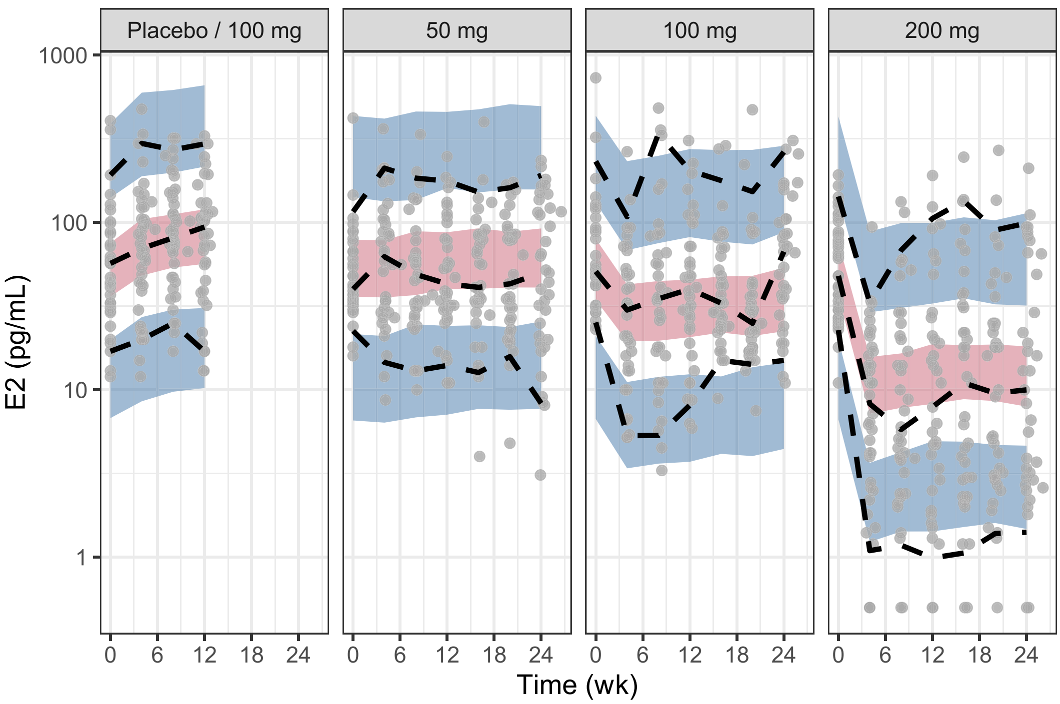

FIGURE 3 Visual predictive check for pharmacokinetic–oestradiol (E2) model. The final pharmacokinetic–E2 model was used to repeatedly re-simulate data from the EDELWEISS trial. The blue bands show 95% prediction intervals around the 5th and 95th percentiles of the simulated replicates. The red band shows the 95% prediction interval for the median simulated value. Dashed lines show the median, 5th and 95th percentiles of the observed E2 data from EDELWEISS (E2 observations shown with grey points)

TABLE 6 Parameter estimates for the final dysmenorrhoea (DYS) and nonmenstrual pelvic pain (NMPP) models. Estimates correspond to the odds ratio of pain reduction except the intercept, which corresponds to the odds of pain reduction

	DYS VRS pain		NMPP VRS pain	
Covariate	**Estimate***	**95% CI**	**Estimate***	**95% CI**
Intercept (odds)	6.27	1.46–26.9	0.326	0.0937–0.559
Baseline pain	1.23	0.367–4.13	0.987	0.966–1.01
Non-Caucasian	253	29.9–2140	2.4	1.47–3.33
Weight	0.966	0.909–1.03	5.94	3.57–8.31
Days 29–56	47.2	7.58–294	9.17	5.41–12.9
Days 57–84	75.9	11.1–518	17	9.77–24.3
Days 85–112	6.29	1.10–36.1	16.1	9.21–23.0
Days 113–140	23.9	3.57–160	0.987	0.978–0.995
Days 141–168	8.21	1.39–48.4	0.326	0.0937–0.559
E2	0.703	0.474–1.04	0.987	0.966–1.01
Baseline pain × E2	1.10	0.805–1.50		
Non-Caucasian × E2	0.294	0.169–0.512		
Weight × E2	1.00	0.988–1.02		
Days 29–56 × E2	0.362	0.225–0.583		
Days 57–84 × E2	0.355	0.217–0.580		
Days 85–112 × E2	0.733	0.465–1.16		
Days 113–140 × E2	0.503	0.308–0.823		
Days 141–168 × E2	0.665	0.419–1.05		

Abbreviations: CI, confidence interval; E2, oestradiol; VRS, verbal rating scale.

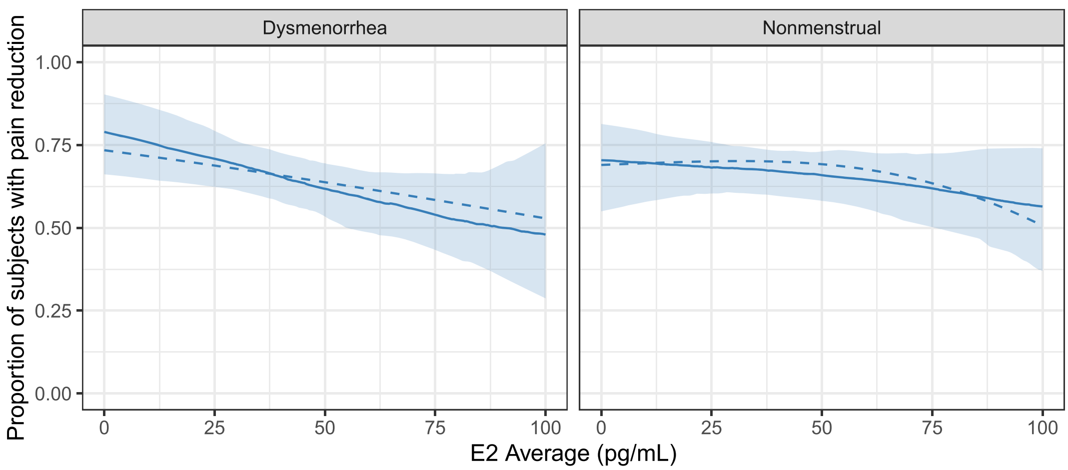

FIGURE 5 Visual predictive check of dysmenorrhoea and nonmenstrual pelvic pain endpoints at 24 weeks of Caucasian patients. Dashed and solid lines are observed and simulated data. Shaded areas are 95% prediction intervals of simulations. Observed data within the prediction interval indicates that the final model provides a good description of observed data. E2: oestradiol

24 LS BMD change from baseline ranged from −0.092% in the 50 mg dose, −1.30% in the 100 mg dose group, and −2.67% in the 200 mg dose group. All structural model parameters were fixed to values reported in Riggs *et al.*[9] and only parameters in the E2 scaling function were estimated (see Equation 6 from Riggs *et al.*[9] and Table 8). The model was able to describe these dose-dependent changes in LS BMD at the 12- and 24-week visits (Figure 7).

3.2 | Dose selection

3.2.1 | Efficacy simulations (DYS, NMPP)

For a given dose, the final estimated Pop-PK E2 model was used to simulate E2 values at 24 weeks. The simulated E2 values were used to obtain predicted values of pain and bleeding using the final estimated pain and bleeding models accounting for parameter uncertainty

(Figure 8). These predicted values were used to compute the probability of achieving a target response or better. For Caucasian patients, the probability of surpassing the NMPP target was over 95% for doses ≥50 mg (Figure 9). For DYS, the probability of surpassing the DYS target was over 95% at doses of 75 mg or greater.

TABLE 7 Parameter estimates for the final uterine bleeding model. Estimates correspond to odds ratios except for intercept parameters, which correspond to odds

	Bleeding	
Parameter	odds ratio	95 % CI
Mean		
Intercept (odds)	0.120	0.109–0.134
Baseline bleeding/pain	6.01	4.25–8.58
Non-Caucasian	1.08	1.02–1.16
Healthy	0.714	0.631–0.800
Weight	0.968	0.951–0.988
Days 29–56	1.179	1.09–1.29
Days 57–84	1.13	1.03–1.24
Days 85–112	1.17	1.07–1.28
Days 113–140	1.21	1.09–1.35
Days 141–168	1.23	1.13–1.35
E2	1.04	1.02–1.06
Dispersion		
Intercept (odds)	0.196	0.163–0.235
Baseline bleeding/pain	4.19	1.79–9.08
E2	0.926	0.872–0.994
Probability of 0		
Intercept (odds)	0.683	0.528–0.878
Baseline bleeding/pain	0.0916	0.0307–0.226
Non-Caucasian	0.421	0.390–0.457
Days 29–56	1.33	1.05–1.69
Days 57–84	1.39	1.10–1.71
Days 85–112	1.33	1.07–1.69
Days 113–140	1.50	1.18–1.93
Days 141–168	1.52	1.19–1.96
E2	0.683	0.528–0.878

Abbreviation: CI, confidence interval.

3.3 | Safety simulations (BMD)

Simulations from the E2-BMD model under different candidate doses in a Caucasian population are shown in Figure 10. Doses between 75 and 150 mg daily were associated with week 24 E2 concentrations in the proposed target window of 20–50 pg/mL. Furthermore, doses <100 mg daily were expected to result in LS BMD declines that do not exceed −1.6% at week 24.

3.4 | Integrated simulations

Linzagolix doses of 75 to 100 mg daily are expected to meet the decision target with high (>95%) probability for efficacy (DYS, NMPP) and safety (BMD) endpoints (Figure 9).

4 | DISCUSSION

Pharmacotherapy has a pivotal role in symptom-relief for endometriosis, an oestrogen-dependent gynaecological condition. The GnRH

TABLE 8 Parameter estimates for the final bone mineral density (BMD) model. All parameter estimates were derived from patients enrolled in the EDELWEISS trial. The 95% confidence intervals (CI) were calculated from 500 bootstrap replicates

Parameter	Value	95% CI
Structural parameters		
BMD E2-transform $E2_{50}$ (pg/mL)	0.202	0.135–0.401
BMD E2-transform sigmoidicity	1.17	0.791–1.93
Residual variability		
Additive error (percent change from baseline)	5.75	5.12–6.42

Abbreviation: CI, confidence interval.

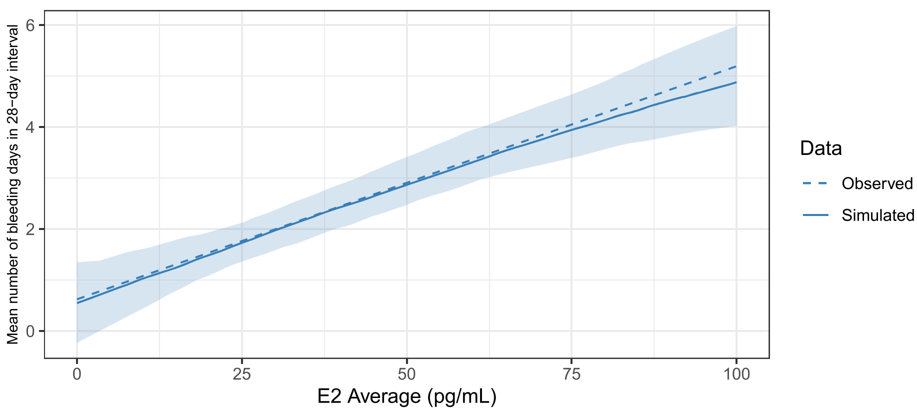

FIGURE 6 Visual predictive check of uterine bleeding at 24 weeks of Caucasian patients. Dashed and solid lines are observed and simulated data. Shaded areas are 95% prediction intervals of simulations. Observed data within the prediction interval indicate that the final model provides a good description of observed data. E2: oestradiol

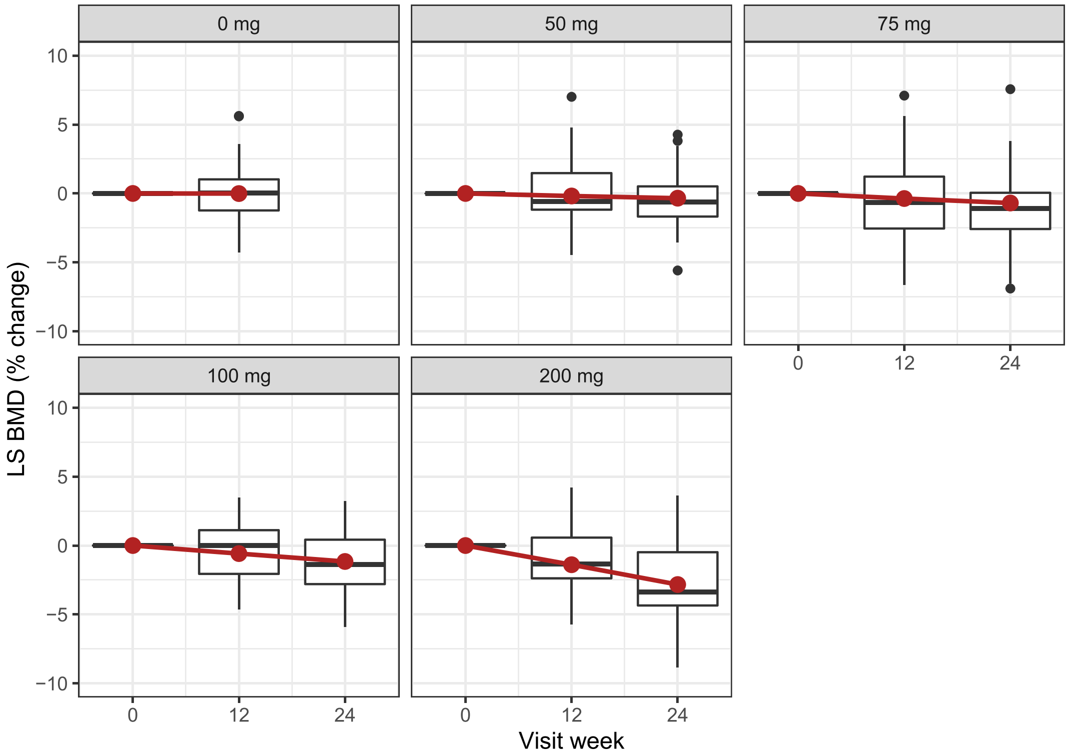

FIGURE 7 Lumbar spine bone mineral density (LS BMD) observed and model-predicted values by linzagolix dose for Caucasian patients enrolled in EDELWEISS. The red lines and points mark the median model predicted values. The boxplots summarize observed LS BMD values at the nominal visit week. Baseline (week 0) LS BMD values are zero by definition and were not included in the model estimation data set; they are included here only for context

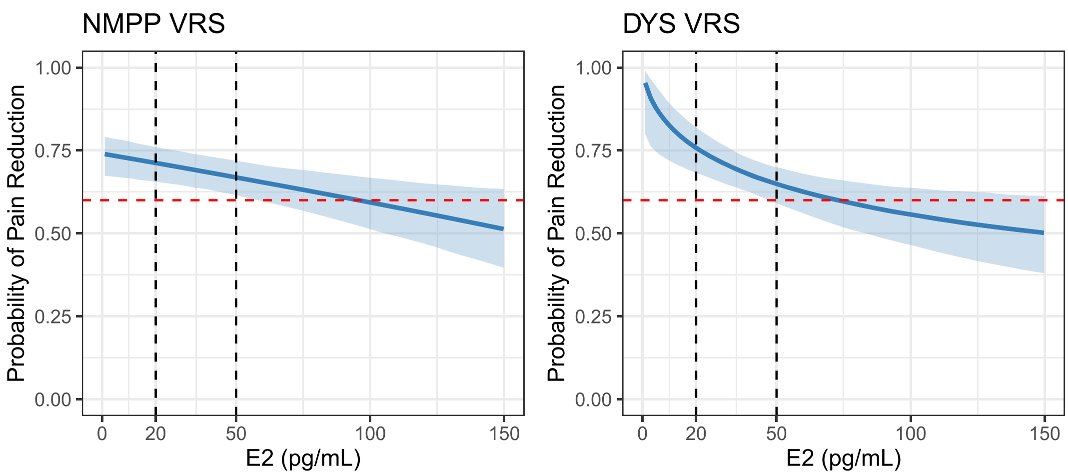

FIGURE 8 Predictions of dysmenorrhoea (DYS) and nonmenstrual pelvic pain (NMPP) pain endpoints at 24 weeks of Caucasian reference patients. Line is median prediction and shaded area is 95% confidence interval. Horizontal red line is target criteria. Vertical dashed lines are values at 20 and 50 pg/mL. Box plot is distribution of oestradiol (E2) for subjects at a given dose. E2: oestradiol; VRS: verbal rating scale

antagonist linzagolix is a promising new potential treatment option. Linzagolix allows dose-dependent control of E2 levels reducing endometriosis-associated pain, but it is associated with hypo-estrogenic adverse effects, including hot flushes and BMD loss, when E2 production is fully suppressed. Models relating pharmacokinetics, pharmacodynamics, and clinical outcomes are routinely used to support dose selection in clinical drug development.[17] Specifically, mechanistic, systems-based modelling has been previously used to balance benefits and risks for GnRH receptor modulators in the treatment of endometriosis.[9] QSP integrates the characteristics of a drug (dose, dosing regimen, or a full pharmacokinetic submodel) with target biology and functional endpoints.[18] The analyses herein used simulated E2 from the derived PK-E2 model to drive efficacy and safety outcomes and support the selection of linzagolix doses for use in Phase 3 studies enrolling Caucasian patients with endometriosis. QSP was particularly useful in this context to explore linzagolix doses that lower E2 to an optimal level for pain relief with minimal BMD losses.

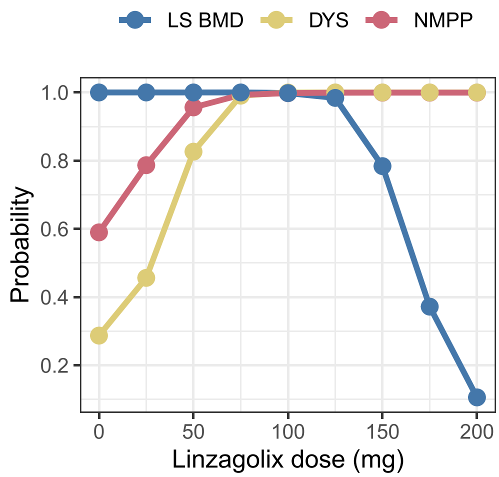

FIGURE 9 Dose selection for Caucasian patients. The probabilities of satisfying the decision targets are shown *vs.* linzagolix daily dose (mg). LS BMD: lumbar spine bone mineral density; DYS: dysmenorrhoea; NMPP: nonmenstrual pelvic pain

Population PK modelling described linzagolix dose–exposure relationships and included weight effects on CL/F and V2/F using fixed allometric scaling values. Overall, estimated PK were similar between Caucasian and non-Caucasian subjects, except for a statistically significant covariate on CL/F that may not be considered clinically significant. After characterizing linzagolix exposure, a model was developed to characterize the relationship between linzagolix exposure and E2 lowering in endometriosis patients and HVs. Linzagolix was found to decrease E2 in an exposure-dependent manner with AUC_{50} of 1.68×10^5 ng h/mL (90% CI: 1.44×10^5 to 1.91×10^5).

Clinical outcome models for pain were developed as a function of modelled E2. As for the BMD submodel, an existing QSP model of bone health was adapted to the needs of this study.[19,20] This model was shown to be valid for bone metabolism and pathologies such as osteoporosis, chronic kidney disease, menopause transition, and hypoparathyroidism.[10] The model was integrated with additional PK models to describe pharmacological effects of parathyroid analogue (teriparatide[21]), calcium sensing receptor modulators,[22] exogenous vitamin D,[23] sclerostin inhibition[24] and receptor activator of nuclear factor-κB ligand inhibition.[19,25]

Decision criteria based on available clinical data for this class of drugs[14,26] were established for efficacy (pain) and safety (LS BMD) endpoints that maximized discrimination between different doses and evaluated 24 weeks after the first dose. In the Caucasian patient population, doses from 75 mg reached efficacy targets with high probability for DYS and NMPP endpoints. As for the BMD target, doses below 150 mg fulfilled the bone safety criterion (Figure 9).

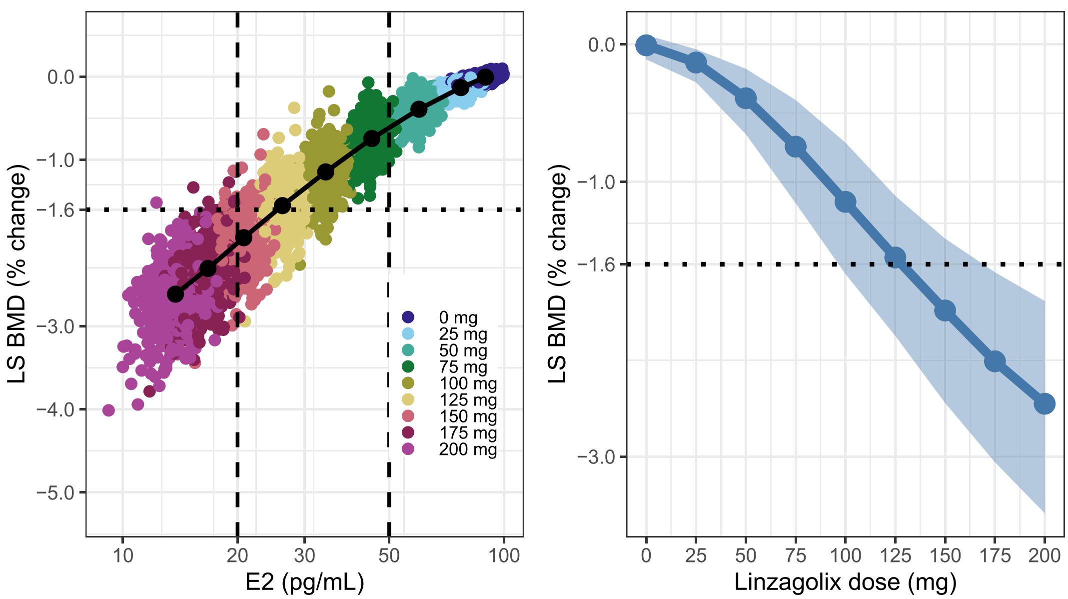

FIGURE 10 Model-based assessment of expected lumbar spine bone mineral density (LS BMD) changes at week 24 in Caucasian patients. pharmacokinetic, oestradiol (E2) and LS BMD were simulated from the final models at different linzagolix doses, incorporating uncertainty in the fixed effect parameter estimates only. $n = 500$ parameter sets were used for the simulation. Horizontal reference lines indicate week 24 BMD target (−1.6% change from baseline). (A) LS BMD *vs.* E2. The vertical dashed reference lines mark E2 values of 20 and 50 pg/mL. (B) Simulated LS BMD *vs.* linzagolix dose. The line and points mark the median simulated percent change from baseline and the shaded area indicates the 95% prediction interval

Linzagolix was also effective in reducing bleeding at all doses, with higher doses showing greater reduction in proportion of bleeding days (Figure 6). Since there were no prespecified targets for uterine bleeding, an approach when comparing doses is to consider the highest linzagolix dose which does not negatively impact BMD. For the described patient population, 100 mg (a dose expected to satisfy the pain and safety decision target) is estimated to reduce the number of bleeding days by 60% relative to baseline. In addition to the endometriosis indication, linzagolix may control heavy menstrual bleeding in patients with other hormone-dependent conditions such as uterine fibroids, common benign oestrogen-sensitive tumours in the uterus.[27] A recent study of another GnRH receptor antagonist has shown dose-dependent efficacy in patients with uterine fibroids.[28] However in this analysis, there was not sufficient available data to properly differentiate the bleeding efficacy of linzagolix in endometriosis patients with co-existing uterine fibroids compared to endometriosis-only patients. Understanding exposure-response relationships for linzagolix with the current work may help support future dose selection for the uterine fibroid indication as well as potential to extrapolate to other patient populations.

Another objective for the analysis was to evaluate the viability of E2 as a surrogate for the efficacy and safety endpoints in the Caucasian populations. The term *surrogate* is used here in a non-technical sense, only to indicate that effective and safe therapy with linzagolix could potentially be inferred if E2 values are lowered into a validated target range. The proposed E2 target range of 20–50 pg/mL appeared to align fairly well with meeting targets for DYS pain and, to a lesser degree, NMPP (Figure 8). Targeting the E2 concentration of 20–50 pg/mL was also associated with LS BMD reductions that generally did not exceed the target of −1.6% at 24 weeks for Caucasian patients (Figure 10).

Overall, the previously reported E2 target range (20–50 pg/mL) to balance efficacy and safety endpoints was confirmed. Linzagolix doses between 75 and 125 mg daily were expected to meet pain and BMD targets in Caucasian endometriosis patients. The dose level selected for confirmatory linzagolix Phase 3 studies in endometriosis (NCT03992846, NCT03986944)[29,30] was 75 mg once daily, and is thus a safety-oriented choice within the identified optimal dose range.

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CONTRIBUTORS

J.-P.G, and O.P. from ObsEva designed the trials, acquired the data, interpreted results, contributed to the writing, and reviewed the manuscript. K.B., M.R., J.F. and R.G. from Metrum Research Group planned and conducted all data analyses, interpreted results, contributed to the writing, and reviewed the manuscript.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

1. Giudice LC. Endometriosis. *N Engl J Med*. 2010;362(25):2389-2398.
2. Bulun SE, Yilmaz BD, Sison C, et al. Endometriosis. *Endocr Rev*. 2019; 40(4):1048-1079. doi:10.1210/er.2018-00242
3. Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Viganò P. Endometriosis. *Nat Rev Dis Primers*. 2018;4(1):1–25. doi: 10.1038/s41572-018-0008-5
4. Reis FM, Petraglia F, Taylor RN. Endometriosis: hormone regulation and clinical consequences of chemotaxis and apoptosis. *Hum Reprod Update*. 2013;19(4):406-418.
5. Johnson NP, Hummelshoj L. World Endometriosis Society Montpellier Consortium. Consensus on current management of endometriosis. *Hum Reprod*. 2013;28(6):1552-1568.
6. Brown J, Pan A, Hart RJ. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. *Cochrane Database Syst Rev*. 2010;2010(12):CD008475.
7. Petta CA, Ferriani RA, Abrao MS, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. *Hum Reprod*. 2005;20(7):1993-1998.
8. Barbieri RL. Hormone treatment of endometriosis: The estrogen threshold hypothesis. *Am J Obstet Gynecol*. 1992;166(2):740-745.
9. Riggs MM, Bennetts M, van der Graaf PH, Martin SW. Integrated pharmacometrics and systems pharmacology model-based analyses to guide GnRH receptor modulator development for management of endometriosis. *CPT Pharmacometrics Syst Pharmacol*. 2012; 1:e11.
10. Riggs MM, Cremers S. Pharmacometrics and systems pharmacology for metabolic bone diseases. *Br J Pharmacol*. 2019;85(6):1136-1146.
11. Donnez J, Taylor HS, Taylor RN, et al. Treatment of endometriosis-associated pain with linzagolix, an oral gonadotropin-releasing hormone-antagonist: a randomized clinical trial. *Fertil Steril*. 2020; 114(1):44-55.
12. Pohl O, Marchand L, Bell D, Gotteland J-P. Effects of combined GnRH receptor antagonist linzagolix and hormonal add-back therapy on vaginal bleeding-delayed add-back onset does not improve bleeding pattern. *Reprod Sci*. 2020;27(4):988-995. doi: 10.1007/s43032-020-00172-z
13. Lo JC, Burnett-Bowie S-AM, Finkelstein JS. Bone and the perimenopause. *Obstet Gynecol Clin North Am*. 2011;38(3):503-517.
14. Taylor HS, Giudice LC, Lessey BA, et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. *N Engl J Med*. 2017;377(1):28-40.
15. Carr BR, Stewart EA, Archer DF, et al. Elagolix Alone or With Add-Back Therapy in Women With Heavy Menstrual Bleeding and Uterine Leiomyomas: A Randomized Controlled Trial. *Obstet Gynecol*. 132(5): 1252-1264.

16. Alexander SPH, Christopoulos A, Davenport AP, et al. The Concise Guide to PHARMACOLOGY 2019/20: G protein-coupled receptors. *Br J Pharmacol*. 2019;176(S1):S21-S141.
17. Marshall S, Madabushi R, Manolis E, et al. Model-Informed Drug Discovery and Development: Current Industry Good Practice and Regulatory Expectations and Future Perspectives. *CPT Pharmacometrics Syst Pharmacol*. 2019;8(2):87-96.
18. Helmlinger G, Al-Huniti N, Aksenov S, et al. Drug-disease modeling in the pharmaceutical industry - where mechanistic systems pharmacology and statistical pharmacometrics meet. *Eur J Pharm Sci*. 2017;109: S39-S46. doi:10.1016/j.ejps.2017.05.028
19. Peterson MC, Riggs MM. A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. *Bone*. 2010; 46(1):49-63.
20. A Multiscale Systems Model of Bone Health and Mineral Homeostasis. Github. Accessed July 8, 2020. https://github.com/metrumresearchgroup/OpenBoneMin
21. Peterson MC, Riggs MM. FDA Advisory Meeting Clinical Pharmacology Review Utilizes a Quantitative Systems Pharmacology (QSP) Model: A Watershed Moment? *CPT Pharmacometrics Syst Pharmacol*. 2015;4(3):189-192. doi:10.1002/psp4.20
22. Baron KT, Riggs MM, Sawamura R, et al. An Evaluation of Calcilytic Effects on Parathyroid Hormone and Bone Mineral Density Response Using a Physiologically-Based, Multiscale Systems Pharmacology Model. *J Bone Miner Res*. 2013;28(1):1830–1836.
23. Ocampo-Pelland AS, Gastonguay MR, Riggs MM. Extension of multiscale systems pharmacology model to evaluate effect of vitamin D3 pharmacokinetics on bone health. Presented at the 7thAnnual American Conference on Pharmacometrics (ACOP). Published online 2016.
24. Eudy RJ, Gastonguay MR, Baron KT, Riggs MM. Sclerostin-Mediated Osteocyte Control in Bone Remodeling: Extension of a Multiscale Systems Model to Consider New Therapies for Osteoporosis. In: *Page 24*. Vol Abstr 3355; 2015.
25. Peterson MC & Riggs MM Predicting Nonlinear Changes in BMD Over Time using a Physiologically-Based Mathematical Model. In: Presented at American Association of Pharmaceutical Scientists National Biotechnology Conference, Update on Quantitative Systems and Disease Models for Biologics. Mini-Symposium. 2010.
26. AbbVie, Inc. ORILISSA™ (elagolix) Tablets, for Oral Use: Highlights of Prescribing Information. Published 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210450s000lbl.pdf
27. Pohl O, Marchand L, Fawkes N, Gotteland J-P, Loumaye E. Gonadotropin-Releasing Hormone Receptor Antagonist Mono- and Combination Therapy With Estradiol/Norethindrone Acetate Add-Back: Pharmacodynamics and Safety of OBE2109. *J Clin Endocrinol Metab*. 2018;103(2):497-504.
28. Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for Heavy Menstrual Bleeding in Women with Uterine Fibroids. *N Engl J Med*. 2020; 382(4):328-340.
29. ObsEva SA. Study: Efficacy and Safety of Linzagolix for the Treatment of Endometriosis-associated Pain. (NCT03992846). ClinicalTrials.gov. Accessed July 6, 2020. https://clinicaltrials.gov/ct2/show/NCT03992846
30. ObsEva SA. A Phase 3 Study to Confirm the Efficacy and Safety of Linzagolix to Treat Endometriosis-associated Pain. (NCT03986944). ClinicalTrials.gov. Accessed July 6, 2020. https://clinicaltrials.gov/ct2/show/NCT03986944

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